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PTO/SB/21 (07-06)

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	16

Application Number	10/659,408
Filing Date	September 10, 2003
First Named Inventor	Parikh, Rajiv
Art Unit	1616
Examiner Name	Alstrum-Acevedo, James Henry
Attorney Docket Number	021956-000500US

ENCLOSURES *(Check all that apply)*

- ☒ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
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- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) (please identify below):

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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Townsend and Townsend and Crew LLP		
Signature			
Printed name	M. Henry Heines		
Date	SEPT 07, 2006	Reg. No.	28,219

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PTO/SB/17 (01-06)

Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2006

☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT	($) 250

Complete if Known	
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1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

Total Claims		Extra Claims	Fee ($)		Fee Paid ($)
_____	-20 or HP =	_____	x _____	=	_____

HP = highest number of total claims paid for, if greater than 20

Indep. Claims		Extra Claims	Fee ($)		Fee Paid ($)
_____	-3 or HP =	_____	x _____	=	_____

HP = highest number of independent claims paid for, if greater than 3

Multiple Dependent Claims	
Fee ($)	Fee Paid ($)
_____	_____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets		Extra Sheets		Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
_____	- 100 =	_____	/ 50 =	_____ (round up to a whole number)	x _____	= _____

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge): Filing a brief in support of an appeal	250

SUBMITTED BY

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PATENT
Attorney Docket No. 021956-000500US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 4639
Rajiv PARIKH et al.	Examiner: Alstrum-Acevedo, James Henry
Application No.: 10/659,408	Technology Center/Art Unit: 1616
Filed: September 10, 2003	
For: METHOD FOR TREATING AIRWAY DISORDERS	**APPELLANTS' BRIEF UNDER 37 CFR §41.37**

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal mailed on August 3, 2006 for the above-referenced application, Appellants submit this Brief on Appeal.

TABLE OF CONTENTS

1. REAL PARTY IN INTEREST 3

2. RELATED APPEALS AND INTERFERENCES 3

3. STATUS OF CLAIMS 3

4. STATUS OF AMENDMENTS 3

5. SUMMARY OF CLAIMED SUBJECT MATTER 3

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL 4

7. ARGUMENT 5

8. CONCLUSION 5

9. CLAIMS APPENDIX 10

10. EVIDENCE APPENDIX 12

11. RELATED PROCEEDINGS APPENDIX 13

1. REAL PARTY IN INTEREST

The real party in interest is the assignee, Aperon Biosystems Corporation.

2. RELATED APPEALS AND INTERFERENCES

None.

3. STATUS OF CLAIMS

Claims 1-11 are canceled, claims 12-17 are withdrawn, and claims 18-27 stand rejected. The claims that are being appealed are claims 18-27.

4. STATUS OF AMENDMENTS

No amendments have been submitted subsequent to final rejection.

5. SUMMARY OF CLAIMED SUBJECT MATTER

Persons suffering from pulmonary inflammation, which is the cause of asthma, have long been at a disadvantage in attempting to control the condition, since the degree of inflammation can only be detected by monitoring the symptoms of the inflammation rather than measuring the inflammation directly, and these symptoms tend to vary not only with the degree of inflammation but also with factors that are not related to the inflammation. The symptom that is considered the best indicator of the degree of inflammation is the level of nitric oxide in the exhaled breath of the subject. Factors other than inflammation, therefore, can reduce or cancel elevated levels of nitric oxide. These factors include environmental conditions, contemporaneous treatments for non-asthma-related ailments, and reactions to treatments and to changes in treatments. These factors can be transitory, and voluntary or involuntary, and different individuals will respond in different ways, depending on one's individual immune system and on one's recent history of exposure or treatment. The effects of these extraneous factors obscure the reliability and value of both individual and successive nitric oxide measurements.

The present invention resides in the discovery that by taking repeated nitric oxide measurements on samples of exhaled breath from a given patient over a period of time to determine a trend in the measured nitric oxide levels, and comparing the trend with a baseline that has also been determined by repeated measurements from the same patient over time, one can control the patient's pulmonary inflammation more accurately by modifying the frequency and/or type of treatment on the basis of differences between the measured trend and the baseline. The result provides significantly more effective control of the inflammation than one can obtain from individual measurements and a single target value.

In compliance with 37 CFR § 41.67(c)(1)(v), Appellants offer the following information in regard to claim 18:

Step (a) is supported by the acts described at page 4, lines 19-21, i.e., the establishment of a baseline by the use of normative patient data at the start of therapy.

Step (b) is supported by the acts described at page 6, lines 1-2 and 7-10, i.e., the taking of readings 2-3 times per week for at least seven days to establish a baseline.

Step (c) is supported by the acts described at page 6, lines 22-25, i.e., the detection of a deviation of 5 ppb as a limit, based on an exhalation rate of 50 mL/sec, as a determining factor.

Step (d) is supported by the acts described at page 6, lines 10-15, i.e., the use of a decreasing trend as a factor in determining whether to modify a treatment protocol, and the use of a five-day waiting period after a modification before making further modifications.

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds of rejection to be reviewed on appeal are as follows:

(a) Lack of patentability for obviousness over the combination of Moilanen et al. (US 2002/0193698) and Kharitonov et al. (*Monaldi Arch. Chest Dis.* (1996)). This rejection can be summarized as stating that Moilanen et al.'s disclosure of differences between the level of nitric oxide in the exhaled breath of an asthmatic subject and that of a healthy subject, and of the fact that the level in an asthmatic subject can be controlled with medication, combined with

Kharitonov et al.'s inclusion of the word "monitoring" and the phrases "assessing the anti-inflammatory effect of inhaled asthma treatments" and "absolute values are less important than serial measurement in individual patients" suggest Appellants' detailed baseline-based treatment modification method. The rejection concedes that neither reference discloses either the generation or use of a baseline or any particular means of determining how to modify a treatment, much less one involving the particulars of the modification protocol expressed in the claims on appeal, but nevertheless finds these features obvious over the limited observations of these two references.

(b) Lack of patentability for obviousness over the combination of Hampton et al. (US 2003/0073919) and Moilanen et al. (US 2002/0193698). This rejection can be summarized as stating that the Hampton et al.'s mention of the fact that one *may* take measurements over a period of time of an unrelated analyte and for a host of medical conditions, none of which have anything to do with pulmonary inflammation or asthma, can be combined with Moilanen et al.'s disclosure of the use of medication to lower the level of nitric oxide in the exhaled breath of an asthmatic patient, to render the specific baseline-based method of Appellants' claims obvious.

7. ARGUMENT

(a) Claims 18-27 are nonobvious over Moilanen et al. (US 2002/0193698) in view of Kharitonov et al. (*Monaldi Arch. Chest Dis.* 1996, 51(6), pp. 533-537).

The Moilanen et al. publication is a limited teaching of two "basic ideas" in nitric oxide detections in exhaled breath -- first, that the exhalation flow rate should be controlled at a "predetermined value," second, that the nitric oxide levels should be determined at a number of different flow rates (see paragraph **[0015]** on page 2 of the publication). The purpose of performing determinations at different flow rates is to allow the clinician to "draw conclusions on the intensity and location of the inflammation in the lungs" see page 3, last sentence of paragraph **[0027]**. Different flow rates are therefore used to differentiate between bronchial NO flux and alveolar NO concentration. This is explained in paragraphs **[0030]** and **[0031]** of page 3. The final rejection notes that Moilanen et al. mention an eight-week test, but there is no mention of generating a baseline or of using a baseline in any particular way as a basis for

treatment modifications. While Moilanen et al. *might* have been able to derive a baseline from measurements taken over eight weeks, they do not report having done so, and they also fail to disclose the making of any adjustments to the treatment protocol after comparing the results with a baseline or with deviations from a baseline.

The final rejection quotes without comment the following statement from paragraph **[0031]** of Moilanen et al.:

> "The results also suggest that the present method can be used to follow-up drug treatment of inflammatory lung diseases and provide means to assess the efficacy of such treatment."

Despite the lack of comment, the quote is apparently intended to address steps (c) and (d) of the method recited in Appellants' claim 1. The "present method" in this statement refers to the measurement at different exhalation rates to correlate the data with specific locations in the subject's respiratory system, as explained above. There is no suggestion in this statement of the frequency of the measurement needed to establish the baseline, or of the frequency or number of measurements over any period of time to determine the amount or direction of the change in measured NO levels, much less any tailoring of modifications of the treatment based on the degree and the direction of the change. The criticality of the time periods in establishing the baseline and in evaluating the drifts, as recited in Appellants' claims, is not mentioned or suggested. Neither this protocol nor the process as a whole as presently claimed by Appellants are either disclosed or suggested by Moilanen et al.

The Kharitonov et al. paper discloses the use of exhaled NO for "monitoring" (p. 533, left col.) and "assessing the anti-inflammatory effect of inhaled asthma treatments" (p. 535, right col.), and states that "absolute values are less important than serial measurement in individual patients" (p. 536, left col.). There is no discussion of a comparison of detected values with a baseline, of the particular results that should initiate a modification, or of how the modification should be monitored. Nor is there sufficient disclosure to enable the person skilled in the art to take measurements and process them in the manner recited in the claims on appeal. The claims on appeal recite parameters that are specifically directed to achieving control in any individual regardless of the environment or of any aberration or special circumstance in the

individual's recent physiological history that might affect the measurement. By simply referring to "monitoring" and "serial measurement," Kharitonov et al. do not lead one to such features as a minimum frequency of measurement and a minimum length of time to allow a treatment modification to affect the subject's condition before considering further modification to the treatment protocol. By their own admission, Kharitonov et al. rely on "precise" measurement (p. 536, left col.), which indicates individual measurements rather than the generation of a baseline and the comparison of a series of repeated measurements to the baseline.

To summarize, neither Moilanen et al. nor Kharitonov et al. disclose or suggest the frequency of the measurement needed to establish the baseline, or the frequency or number of measurements over any period of time to determine the amount or direction of the change in measured NO levels, much less any tailoring of modifications of the treatment based on the degree and the direction of the change. All of these features are recited in the claims on appeal.

(b) Claims 18-24 are likewise nonobvious over Hampton et al. (US 2003/0073919) in view of Moilanen et al. (US 2002/0193698)

As a preliminary matter, the relevance of Hampton et al. as prior art relative to the subject matter of the claims on appeal is highly questionable, since Hampton et al. is strictly limited to carbon dioxide while the claims on appeal are strictly limited to nitric oxide. The respiratory conditions giving rise to abnormalities in the amount of carbon dioxide in exhaled breath are not coextensive with those relating to elevated levels of nitric oxide, and the treatment protocols and response to treatment differ as well. Nothing in the final rejection or in any of the cited references suggests otherwise. Appellants submit that this reason by itself is justification for reversing this rejection.

Aside from the lack of relevance of Hampton et al. to nitric oxide, the portions of Hampton et al. that are cited in the final rejection as the basis for the rejection of Appellants' claims are paragraphs **[0013]** and **[0015]**, which read as follows (emphasis added):

> "**[0013]** The method *may* take into consideration, for example, the duration of a steady rise of the concentration of carbon dioxide in the breath or the rate of increase of the concentration of carbon dioxide, as measured by the initial angle and slope of the capnogram. The method *may* also compare the carbon dioxide concentration in the

> breath with a characteristic curve. The method *may* further include monitoring the condition of the patient following treatment.
>
> ...
>
> "**[0015]** In a further embodiment, the invention presents a method comprising measuring a concentration of carbon dioxide in a breath expired by a patient and guiding treatment as a function of the measurement. Guiding treatment *may* include determining the presence of lung conditions, determining the severity of the conditions, and selecting medications to treat the conditions."

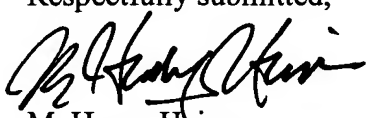
With their equivocal nature and lack of any detail, the statements in these paragraphs do not constitute an "enabling description," i.e., they fail to supply the reader with sufficient information or direction to enable the reader to actually perform the tasks referred to in the paragraphs, and particularly of how to determine whether a rise is significant and how it compares to a baseline. The description in paragraph **[0013]** recognizes only a "steady rise" in analyte concentration rather than a rise defined by the rate of rise at a particular exhalation rate and the duration of the rise. Also, the "characteristic curve" of paragraph **[0013]** is neither explained, illustrated, nor demonstrated. The determinations that a person skilled in the art would have to make in order to perform the indicated tasks to any degree of effectiveness for any analyte, much less one that is not even mentioned in the document, would amount to an independent action of invention.

Features of the present invention that are missing from Hampton et al. are likewise missing from Moilanen et al. who make no mention or suggestion of generating a baseline, comparing measurements taken three times per week for at least seven days to the baseline, and making modifications to the treatment when deviations from the baseline exceed 5 ppb based on an exhalation rate of 50 mL/sec. These features, all of which are recited in the claims on appeal, are not suggested by a disclosure (as in Moilanen et al.) of taking different measurements at different flow rates to detect nitric oxide emissions from different tissues.

8. CONCLUSION

For these reasons, Appellants respectfully submit that the invention as recited in the claims on appeal is patentably novel and nonobvious over the prior art, and request reversal of both rejections.

Respectfully submitted,



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9. CLAIMS APPENDIX

Claim 18: A method for managing a respiratory condition characterized by inflammation of air passageways in a subject who is undergoing treatment for said condition, said method comprising:

(a) establishing a baseline range of nitric oxide concentration in said exhaled breath, said baseline range representing said condition being under control in said subject;

(b) measuring nitric oxide concentrations in a series of samples of exhaled breath taken from said subject at a measurement frequency of at least three times per week over a period of at least seven days, and comparing said nitric oxide concentrations so measured to said baseline range;

(c) if said nitric oxide concentrations so measured are within said baseline range or deviate therefrom by less than 5 ppb based on an exhalation rate of 50 mL/sec, or if said nitric oxide concentrations exceed the upper limit of said baseline range by 5 ppb or more based on an exhalation rate of 50 mL/sec but indicate a decreasing trend, continuing said treatment without change; and

(d) if said nitric oxide concentrations so measured exceed said upper limit by 5 ppb or more without indicating a decreasing trend, modifying said treatment and measuring nitric oxide concentrations in further samples of exhaled breath at said frequency for at least five days and repeating step (c) as necessary to bring said nitric oxide concentration within said baseline range or deviating therefrom by less than 5 ppb based on an exhalation rate of 50 mL/sec.

Claim 19: The method of claim **18** wherein said baseline range has an upper limit of 30 ppb and a lower limit of 20 ppb, based on an exhalation rate of 50 mL/sec.

Claim 20: The method of claim **18** wherein said baseline range has an upper limit of 40 ppb and a lower limit of 20 ppb, based on an exhalation rate of 50 mL/sec.

Claim 21: The method of claim **18** wherein said measurement frequency is once every two days.

Claim 22: The method of claim **18** wherein said measurement frequency is once per day.

Claim 23: The method of claim **18** wherein said treatment comprises administration of medication at a selected dosage, and said modifying of said treatment in step (d) comprises increasing said dosage.

Claim 24: The method of claim **18** wherein said treatment comprises administration of medication at a selected frequency of administration, and said modifying of said treatment in step (d) comprises increasing said frequency.

Claim 25: The method of claim **18** wherein said treatment comprises administration of a medication, and said modifying of said treatment in step (d) comprises changing said medication.

Claim 26: The method of claim **18** wherein step (a) comprises obtaining said baseline range from data obtained from said subject.

Claim 27: The method of claim **18** wherein step (a) comprises obtaining said baseline range from normative patient data not specific to said subject.

10. EVIDENCE APPENDIX

None.

11. RELATED PROCEEDINGS APPENDIX

None.